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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,358	07/10/2006	Kevin Liu	K0001-502-US	7246

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EXAMINER	
O'DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
10/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,358	LIU ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *125-144* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *125-144* is/are rejected.

7)☒ Claim(s) *125* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/30/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application is a 371 of PCT/US04/10737 filed 04/07/2004 which claims benefit to the following U.S. provisional applications: 60/461,574 filed 04/07/2003; 60/461,606 filed 04/07/2003; 60/461,586 filed 04/07/2003.

Claims 125-144 are pending. 2. Applicant is reminded that 37 CFR 1.121 which governs claim amendments states in section (c):

"In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered)."

The status of claim 144 was listed as previously presented in the claim amendments of January 29, 2008, however claim 144 has been amended by the addition of a proviso as shown below:

e) acyl and sulfonyl;

and wherein at least one of R_1 and R_2 is not methyl or ethyl;

Each R_3 is independently selected from the group consisting of

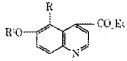
2. Response to Election/Restrictions

Applicant's election of Group II and the species (Example 3B: [5-{3-[(2,4-Bis-trifluoromethyl-benzyl)-(5- ethyl-pyrimidin-2-yl)-amino]-propoxy} - 1 -methyl-indol-3-yl)-acetic acid) in the reply filed on January 29, 2008 is acknowledged. The election was made with traverse, and the examiner finds the arguments unpersuasive. The traversal is on the grounds that the examiner failed to show that the inventions were distinct and also failed to show search burden. The examiner respectfully submits that neither search burden nor a specific finding of distinctness is required in this national stage application filed under 35 U.S.C. 371, rather it is the presence of a special technical feature. To again quote the Patent Cooperation Treaty Language:

Further defining (B), Annex B, **Part 1(f)(i-iii)**, the common structure must; a) occupy a large portion of their structure, or b) the common structure constitutes a structurally distinctive portion, or c) where the structures are equivalent and therefore a recognized class of chemical compounds, each member could be substituted for one another with the same intended result. That is, with a common or equivalent structure, there is an expectation relationship and the corresponding special technical feature result from a common (or equivalent) structure that is responsible for the common activity (or property). **Part 1(f) iv**, indicates that when all alternatives of a Markush grouping can be differently classified, it shall not, taken alone, be considered justification for finding a lack of unity. **Part 1(f)v**, indicates that
"When dealing with alternatives, if it can be shown that at least *one* Markush alternative is not novel over the prior art, the question of unity of invention shall be reconsidered by the examiner"

In the instant case, the examiner had shown that at least one Markush alternative was not novel because prior art RICE L MET AL: "Xanthoquininic Acid Derivatives" JOURNAL OF MEDICINAL CHEMISTRY, vol. 14, no. 4, 1971, pages 369-370, formula II on page 369, column 2 and compound 10 In table 1 on page 370, recites the compounds of the instant case (cited in the international search report)

TABLE I
XANTHOQUININIC ACID DERIVATIVES



10	H	3-Diethylaminopropyl	172–175	$C_{18}H_{28}ClN_3O_3$	C, H, N

Thus the lack of a special technical feature was readily apparent. It is noted that the applicant has amended the claims by proviso in an apparent effort to show unity of invention. The lack of unity was performed on the claims as presented originally. The examiner does not determine

unity of invention *de novo* each time new claims are presented during the course of prosecution, but rather considers only those claims that were present at the time of first action. Regardless

even if the examiner were to follow U.S. restriction practice, the circular object,  , results in so many different ring structures that have markedly different properties and require so many different fields of search that the "unity of invention", à la *In re Weber* 198 USPQ 328 (CCPA 1978) and *In re Watkinson* 14 U.S.P.Q. 2d 1407(Fed. Cir. 1990). M.P.E.P 803.02 referred to in the remarks of January 29, 2008 pg. 9, cannot be considered to have been met. The examiner has however expanded the group definition of R2 to include "monocyclic or bicyclic moiety in which at least one ring atom is nitrogen", in order to reduce the burden on the applicant of filing divisional applications. This in effect reduces the number of compound groups from XIII to III. This application contains claims drawn to a nonelected invention with traverse. A complete reply to this action must include a cancellation of nonelected claims or other appropriate action.

Under Examination:

Group II, Claims 125-144 drawn to compounds reading on claim 125 Formula I where the circular object with a nitrogen atom is indole, R1 is alkyl or benzyl, R2 is a "monocyclic or bicyclic moiety in which at least one ring atom is nitrogen", drawn to indolyl-heteroaryls.

Objections

3. Claim 125 is objected to for the following informalities: It would appear that in the most recent claim amendments for the group a) the recitation "ultra" was inadvertently introduced to replace "nitro". Since "ultra" does not refer to any chemical functional group and the claim previously recited "nitro" in this instance, the examiner takes this to be a transposition error and suggests that "nitro" be added in its place or the term "ultra" removed. In addition, in the definition of R3, c) is recited as "aiyl", this appears to have been an unintentional misspelling of "aryl" and has been treated as such. Appropriate correction is required.

Specification

4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

5. Applicant is reminded of the proper content of an Abstract of the Disclosure. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. Complete revision of the content of the abstract is required on a separate sheet. Currently the abstract mentions only compounds without any specific details as to what the compounds are.

Claim Rejections - 35 USC § 112 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 126-144 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 126 recites the limitation "Ar2" and "R5", however in claim 125 no such variables are listed. There is insufficient antecedent basis for this limitation in the claim.

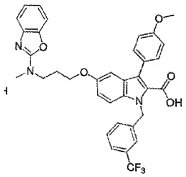
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

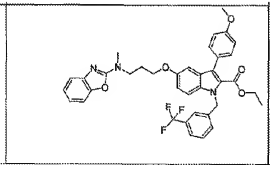
> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claim 125 is rejected under 35 U.S.C. 102(a) as being anticipated by Stolle et. al. WO 2002030895 A1 (cited on the IDS). Stolle discloses the following two compounds, one on pg. 28 and another on pg. 105 compound 159:



159



Instant claim 125 covers these compounds when R4 is alkyl or H, L is a bond, the circular object N is indole, R2 is benzoxazole ("a bicyclic aromatic moiety in which at least one ring atom is nitrogen"), R1 is alkyl, k is 2 and one R3 is phenyl optionally substituted with alkoxy, and the other R3 is alkyl optionally substituted with phenyl ("optionally substituted carbocyclic") AKA benzyl.

8. Claim 125 is rejected under 35 U.S.C. 102(e) as being anticipated by Stolle et. al. U.S. 6,787,651. Stolle discloses the two compounds as shown above in this action at 7, (on column 23 and column 140) that anticipate the instant claims.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

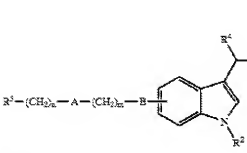
9. Claims 125-144 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodman WO 2001/58893 OR U.S. 6,743,810 AND Lu WO2002/060438, in view of Wolff, M.E. *Burger's Medicinal Chemistry 4th Ed. Part I*, Wiley: New York, **1979**, 336-337. The Goodman. WO 2001/58893 reference is in German and the examiner will rely on the English language U.S. patent 6,743,810 that issued from a national stage entry of the former. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

(MPEP 2141.01)

Goodman et. al. teaches a genus of compounds that are integrin inhibitors and are nearly identical to the compounds of the instant claims. These compounds are described generically at columns 1 and 2:

The invention relates to indol-3-yl derivatives of the formula I



I

in which

A and B are each, independently of one another, O, S, NH, NR^7, CO, CONH, NHCO or a direct bond,

X is alkylene having 1 to 2 carbon atoms which is unsubstituted or monosubstituted by R^4 or R^5, or a direct bond,

R^1 is H, Z or —$(CH_2)_o$—Ar,

R^2 is H, R^7 or —C(O)Z,

R^3 is NHR^6, $—NR^6—C(=NR^6)—NHR^6$, $—C(=NR^6)—NHR^6$, $—NR^6—C(=NR^6)—NHR^6$, $—C(=NR^6)—NHR^6$ or Het^2,

R^4 and R^5 are each, independently of one another, H, oxo, R^7, $—(CH_2)_o—Ar$, $—C(O)—(CH_2)_o—Ar$, $—C(O)—(CH_2)_o—R^7$, $—C(O)—(CH_2)_o—Het$, Het, NHR^6, NHAr, NH—Het, CONH—R^7, CONH—$(CH_2)_o—Ar$, CONH—$(CH_2)_o$—Het, OR^7, OAR, OR^6 or O—Het,

R^6 is H, —C(O)R^7, —C(O)—Ar, —C(O)—Het, R^7, $COOR^7$, COO—$(CH_2)_o$—Ar, COO—$(CH_2)_o$—Het, SO_2—Ar, SO_2R^7 or SO_2—Het,

R^7 is alkyl having 1 to 10 carbon atoms or cycloalkyl having 3 to 10 carbon atoms,

R^8 is Hal, NO_2, CN, Z, $—(CH_2)_o—Ar$, $COOR^1$, OR^1, CF_3, OCF_3, SO_2R^1, NHR^1, $N(R^1)_2$, NH—C(O)R^1, $NHCOOR^1$, COOH, COOZ or C(O)R^1,

R^9 is CN or NO_2,

Z is alkyl having 1 to 6 carbon atoms,

Ar is aryl which is unsubstituted or monosubstituted or polysubstituted by R^8,

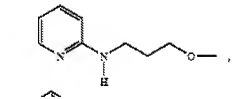
Hal is F, Cl, Br or I,

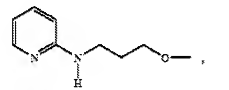
Het is a saturated, partially or fully unsaturated monocyclic or bicyclic heterocyclic radical having 5 to 10 ring members, where 1 or 2 N and/or 1 or 2 S or O atoms may be present and the heterocyclic radical may be monosubstituted or disubstituted by R^8,

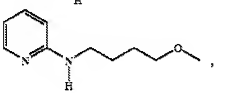
Het^1 is a saturated, partially or fully unsaturated monocyclic or bicyclic heterocyclic radical having 5 to 10 ring members and 1 to 4 N atoms which may be unsubstituted or monosubstituted or disubstituted by Hal, R^7, OR^7, CN, NHZ, oxo or NO_2,

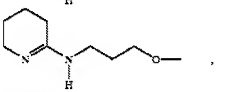
Most striking are the preferred embodiments of Goodman M. et. al., which correspond to the O-$CH_2CH_2CH_2ONR_1Ar_2$ group and in claim 127 of the instant where Ar_2 is pyrimidinyl or pyridine. The portion of column 8, line 41 and following is shown below for clarity:

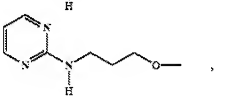
Preferred versions of the substituent R^3—$(CH_2)_n$—A—$(CH_2)_m$—B— are

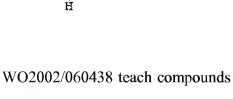






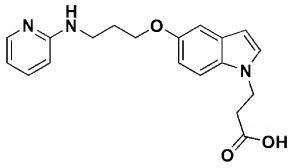




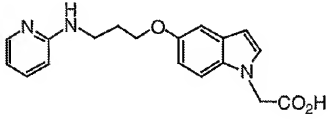


Lu e. al. WO2002/060438 teach compounds that are also integrin inhibitors (the same utility as Goodman) where the position of the acid group on the indole has been moved (i.e. position isomers), two such compounds are Example 1 (pg. 56 and Example 2, pg. 59)

EXAMPLE 1



EXAMPLE 2



These two compounds of Lu (Example 1 and Example 2) shown above differ only by the length of the alkyl chain between the indole and the carboxylic acid group.

Berger teaches that the variation of alkyl chain length, i.e. homologation, in active pharmacological agents is a common modification in medicinal chemistry, (See the examples in Table 8.2 of a local anesthetic SAR pg. 337 of Wolff)

Ascertainment of the difference between the prior art and the claims

It is clear that the prior art compounds differ from those of the instant claims by a single methylene unit (-CH_2-). This is shown graphically in Figure 1.

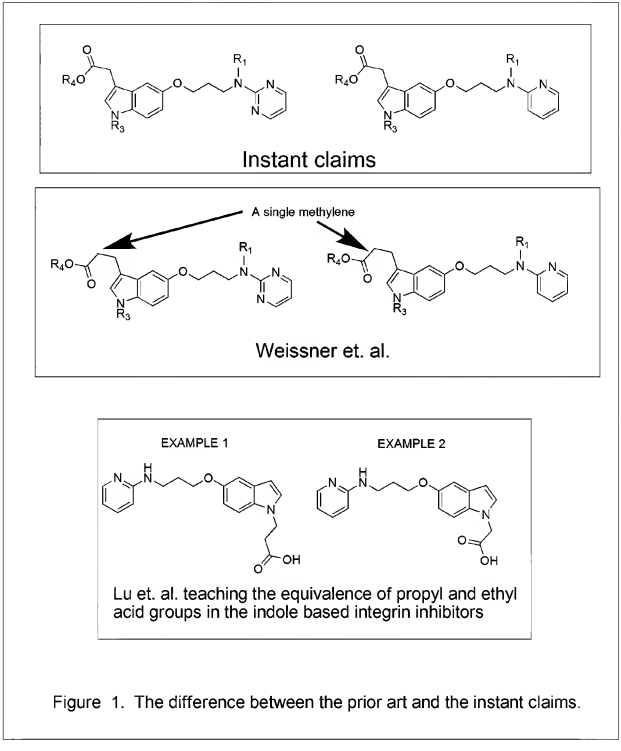


Figure 1. The difference between the prior art and the instant claims.

(MPEP 2141.02)
Finding of prima facie obviousness
Rational and Motivation
(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use analogs of those of Goodman et. al. to produce the instant invention. Analogs differing only in the presence of single methylene, are prima facie obvious and require no secondary teaching. It is well known that alkyl chain homologation is a common change in the design of drugs, as shown by Burger, and thus require no secondary teaching. However, the examiner provides the Lu teaching to show the fact that such modifications were known in this very narrow field of indole based integrin inhibitors. The experienced Ph.D. medicinal chemist, who would make applicants' compounds, would be motivated to prepare these compounds on the expectation that such close analogues would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. It would be routine for the chemist to insert or remove a single methylene group in order to increase potency and to establish better patent protection for his/her compounds. See *In re Coes, Jr.* (CCPA 1949) 173 F2d 1012, 81 USPQ 369. The subgeneric claims drawn to the various definitions of R1 are all included within the generic teaching of Goodman at least where R1 is alkyl (see the definition of R7 of Goodman). It is also noted that the alkyl is only ever "optionally substituted" so the various definitions i.e. where R1 is an alkyl substituted with a carbocycle such as phenyl (i.e. benzyl, claim 127-144) are never a real limitation since it is in fact optional. Claim 136-144 state that R5 is various alkyl groups however these compounds are also included within the generic teaching of Goodman (see Goodman the definition of Het1, when R7 is alkyl).

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable

expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 125 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The proviso introduced in the claim amendments filed on January 29, 2008 describes a genus that was not previously described.

11. Claims 125-144 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, it does not reasonably provide enablement for making prodrugs, pharmaceutically active metabolites, or solvates of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the

predictability or unpredictability of the art, h) and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546.

Prodrugs

a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation. b) The direction concerning the prodrugs is not found in the specification. c) There is no working example of a prodrug of a compound the formula I. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff

(Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula I of claim 125 as well as the presently unknown list of potential prodrug derivatives embraced by claim 125. Nowhere in the specification are directions given for preparing the "prodrugs" of the claimed compounds. Since the structures of these "prodrugs" are uncertain, direction for their preparation must also be unclear. Directions to a team of synthetic pharmaceutical chemists and metabolism experts of how to search for a "prodrug" hardly constitute instructions to the BS process chemist of how to make such a compound.

Solvates

In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims. g) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent".

Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate. h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula I as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad.

Pharmaceutically Active Metabolites

a) Finding a metabolite is an empirical exercise. Predicting the metabolism of a drug is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism de novo, this is still an experimental science. See Bernard Testa "Predicting drug metabolism: Concepts and challenges" Pure and Applied Chemistry 2004, Vol. 76, No. 5, pp. 907–914. Testa developed a model system and had an extremely high rate of failure:

"For the 10 substrates, 130 first-generation metabolites were predicted and/or seen experimentally. Correct predictions represented 30 % of these reactions, apparently false positives 62 %, and false negatives 8 %."

For a compound to be a metabolite, it must undergo a biochemical transformation, and in order to imagine what this metabolism is, we must know what organism this compound has been introduced in. b) The direction concerning the metabolites is not found in the specification. c) There is no working example of a metabolite of a compound) The nature of the invention is the prediction of metabolite and apparently its subsequent preparation. In addition since they must be pharmaceutically active one would also need to test these materials. Nowhere in the specification are any indications of what the metabolites actually are or are directions given for preparing the metabolites. Since the structures of these metabolites are not known, direction for their preparation must also be unknown. Directions to a team of synthetic pharmaceutical chemists and metabolism experts of how to search for a metabolite hardly constitute instructions to the BS process chemist of how to make such a compound. The artisans making Applicants' metabolites as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula I of claim 125 as well as the presently unknown list of potential metabolites embraced by claim 125.

12. Claims 125-144 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds where in generic claim 1 the acetic acid moiety is attached to the indole in the 1, 2, or 3 position and where the oxypropylamino group is

attached to the indole in the 4, 5, or 6 position and where Ar2 is pyrimidine, pyridine, benzoxazole, or benzothiazole, R1 is alkyl or H, R3 is alkyl or H, R5 is alkyl, haloalkyl, alkoxy, hydroxy, cyano or nitro, it does not reasonably provide enablement for compounds bearing the protracted list of substituents as described in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing all heteroaryls, heterocycles, and numerous optional subsitituents. **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds and such compounds should be active at the PPAR-γ receptor. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic/medicinal chemist. **(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** Each one of the factors **(C, E-H)** will be discussed in light of the scientific literature when such a factor is being directly pointed to a large capital letter referring to the

aforementioned Wands factor will be placed directly after such a remark or explication.

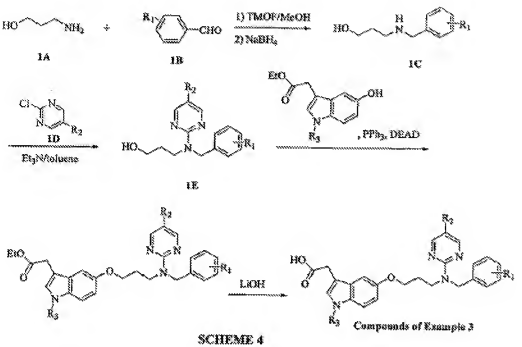
At least in terms of "how to make" the claimed compounds, the chemistry shown does not support the scope claimed. Chemistry in general is an unpredictable area of inquiry and as stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work……Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) [preface]…….even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]…….. As illustrated by the examples discussed below, a good retrosynthesis requires much

> synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures [pg. 3]…….. As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. [8]……..Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, specially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9]…..” Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15. **(E)**

The specification has only a few examples of compounds that were actually prepared (38 compounds reading on the elected indoles as shown on pages 9-12). **(H)** All of these compounds are of a relatively modest scope in terms of the Ar_2, R_5, R_3, R_1 moieties. Outside alkyl the only optional substituents are exemplified only on the benzyl moiety i.e. R_1 and the the Ar_2 moiety and these are meager only alkyl, trifluoromethyl, and methoxy. **(H)**

The applicant has provided a synthesis of the compounds as shown below in Scheme 4, reproduced from the specification page 74, shown below **(F)**:



SCHEME 4

In order to speak to the chemistry directly, the examiner would like to point to deficiencies and problems in reactivity that would not lead one to the full scope of the compounds. The use of Sodium borohydride during reductive amination (1A and 1B to 1C) would reduce the C-X bond in "optionally halogenated alkyls" (where the halogen is Cl, I, or Br) to the alkanes (Hutchins, R.O. et. al. *J. Org. Chem.* **1977**, *42*, 82-91). It is not at all clear to the examiner how these "halogens" could be introduced into the compounds. The SNAr reaction used in the conversion of compound 1C to 1E via reaction with heteroarylhalide 1D is sensitive to electronic substituent effects and generally is not operable where electron rich substituents are present and requires either electronically neutral groups or electron withdrawing groups, See Bunnet, J. F. et. al. "AROMATIC NUCLEOPHILIC SUBSTITUTION REACTIONS" *Chemical Reviews* **1951**, *49*, 273-412, pgs. 307 and following in particular, for example hydroxy and amino deactivate chlorobenzene to the point that no reaction occurs. See Table 14, reproduced below:

TABLE 14

Deactivation by hydroxy and amino groups*
(Clark and Ball (123))

COMPOUND	CONCENTRATION OF METHANOLIC $NaOCH_3$	CHLORINE REPLACEMENT†
	moles per liter	*per cent*
Chlorobenzene	2.0	4
	2.5	7
m-Chlorophenol	2.0	12
o- or *p*-Chlorophenol	2.0	0.0
2,5-Dichloroaniline	1.5	0.0

* Phenolic hydroxy groups are largely ionized under these conditions.
† Treatment for 50–60 hr. at 155°C.

Furthermore, the full scope of 3-acetoxy, 5-hydroxy indoles required as starting materials (Scheme 4, reaction with 1E) are heretofore unknown and cannot be prepared. Despite the applicants reference to numerous indole syntheses each of these reactions have limitations. The Fischer indole synthesis is well known to be sensitive to electronic effects, See Robinson, B. *Chemical Reviews*, **1963**, *63*, 373-401:

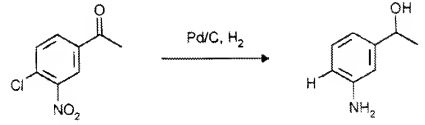
"B. 2-KETOESTER ARYLHYDRAZONES Under Fischer indolization conditions, these compounds undergo cyclization to pyrazolones (CXXXVIII) rather than indolization (125s). " Pg. 394

"E. CYCLOHEXANE-1,2-DIONE MONOARYLHYDRAZONES
The cyclohexane-1,2-dione monophenylhydrazones CXLIII (R = H and CHa, R' = H) are converted by concentrated sulfuric acid not to 1,2,3,4-tetrahydro-1- oxocarbazole (CXLIV, R' = H) and 2,3,4,11-tetrahydro-3,11-dimethyl-l-oxo-lH-carbazole (CXLV, R = CHa, R' = H), respectively, but to the cinnolines (CXLVI, R = H and CH3, R' = H) in 15 and 85% yields, respectively (155" Pg. 394

"Attempts (34) to indolize the m-nitrophenylhydrazones of 3,5-dimethylcyclohex-2-eneone (CXLVII), pulegone (CXLVIII) , and d-carvone (CXLIX) failed, although this failure could be ascribed to the deactivating effect of the nitro substituent in the arylhydrazine moiety," pg. 394 section G

Numerous other examples are found in the review by Robinson. Both the Reissert and von Baeyer indole syntheses referenced on pages 68 and 69 are quite useful but have limitations since a strong reductant must be used to reduce the nitro group. Such conditions are incompatible with the scope of the instant claims and are well known in the art to reduce many functional groups including olefins, nitro groups, halides, cyano groups and ketones all of which are claimed on R_3. See (Tafesh, Ahmed M.; Weiguny, Jens "A Review of the Selective Catalytic Reduction of Aromatic Nitro Compounds into Aromatic Amines, Isocyanates, Carbamates, and Ureas Using CO" *Chemical Reviews* **1996**, *96*, 2035-2052.) where the author states:

> "The selective reduction of nitro aromatic groups in the presence of sensitive functional groups, e.g. carbonyl, cyano, chloro, and alkenic groups, with hydrogen is often difficult, because these sensitive functionalities are reduced faster with hydrogen than the nitro group.[89] Thus when 4-chloro-3-nitroacetophenone **(20)** is subjected to catalytic reduction, the chloro group is reduced (substituted by hydrogen), the nitro group is converted to an amino, and the carbonyl group is hydrogenated to a hydroxy (Figure 12).[90]"



20

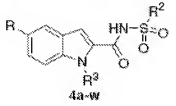
Figure 12.

All chemical syntheses have limitations that prohibit them from being applied at will to any substrate for the synthesis of any compound. While these chemical limitations are real and significant, it is possible to make compounds other than those actually made, however it is also

not possible to use the full scope the claimed compounds. The how to make aspect of 112 1st is important, but 112 1st also requires that one of ordinary skill must be able to use the invention. What are the important structural features for the claimed utility? The specification gives little data for the instantly claimed compounds, and none that would lead one to imagine that the scope claimed has the activity of PPAR-γ binding. **(H)** The medicinal chemistry of indole based PPAR-γ is sensitive to structural changes that may be relatively minor in the chemical sense See Hopkins et. al. "Design and synthesis of novel N-sulfonyl-2-indole carboxamides as potent PPAR-γ binding agents with potential application to the treatment of osteoporosis" *Bioorganic & Medicinal Chemistry Letters* **2006**, *16*, 5659–5663:

"However, when the benzyl group was changed to a benzoyl group all activity was lost (4d vs 4n, 80 nM vs 9400 nM). Alkyl substituents were also not tolerated in this position (4o, 2400 nM)."

Table 3. PPAR-γ binding[11] for *N*-sulfonyl-2-indole carboxamides **4l–t**



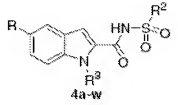
4a-w

Compound	R	R^2	R^3	IC_{50}[a] (nM)
4l	H	3-CF_3-Ph	3-CH_3OBn	140
4m	H	3-CF_3-Ph	3-CF_3OBn	90
4n	H	3-CF_3-Ph	3-CF_3PhCO	9400
4o	H	3-CF_3-Ph	Et	2440
4p	H	3-CF_3-Ph	4-CF_3Bn	400
4q	H	3-CF_3-Ph	3-BnOBn	50
4r	H	3-CF_3-Ph	Bn	280
4s	H	3-CF_3-Ph	2,5-DiClBn	380
4t	H	3-CF_3-Ph	4-*t*-BuBn	330
Rosiglitazone				90
5[12]				80

[a] IC_{50} determinations are the average of three determinations on three separate days.

"Lastly, we investigated substitutions on the phenyl ring of the indole (i.e., R), due to reports in the literature regarding this substituent.7b Keeping R2 and R3 constant, we were interested to see if these compounds would maintain the activity shown for the other compounds (Table 4). Starting from commercially available precursors we were able to obtain compounds 4u–w. Unfortunately, these compounds showed much less activity than the parent R = H compound. Even small substituents (4u, R=Cl and 4u, R = OH) showed a marked loss of binding. "

Table 4. PPAR-γ binding[11] for *N*-sulfonyl-2-indole carboxamides **4u–w**



4a-w

Compound	R	R^2	R^3	IC_{50}[a] (nM)
4u	Cl	3-CF_3–Ph	3-CF_3Bn	330
4v	OBn	3-CF_3–Ph	3-CF_3Bn	770
4w	OH	3-CF_3–Ph	3-CF_3Bn	540

[a] IC_{50} determinations are the average of three determinations on three separate days.

Given the diverse behavior and complete lack of activity for certain groups (even simple modifications such as alkyl as taught by Hopkins), paired with the paucity of information with regard to the synthesis and the molecular determinants of receptor affinity for the compounds of the instant case it is clear from the discussion that the full scope of the claims is not enabled. **(F & G)** In this case the prepared compounds bear a strong structural resemblance to one another, yet the claims are not commensurate in scope. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has only a few working examples in this unpredictable art without undue experimentation. **(C, E, F, G, H).** The examiner would like to point out that while not exemplified, compounds bearing hydroxy, cyano or nitro on the benzyl or heteroaryl ring i.e. R1 and R5, are relatively modest changes and should be achievable and the examiner is not rejecting these materials.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Andres/
Supervisory Patent Examiner, Art Unit 1625

D.K.O.